

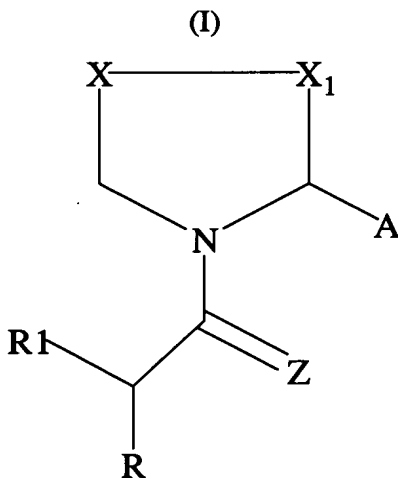
WE CLAIM:

1. An inhibitor of dipeptidyl peptidase IV, wherein the inhibitor comprises a proline mimetic and possesses an  $IC_{50}$  of no more than  $1 \mu m$  and has a molecular weight of no more than 500.

2. The inhibitor according to claim 1, wherein the  $IC_{50}$  is no more than 100 nm.

3. The inhibitor according to claim 1, wherein the inhibitor can be used to treat a central nervous system disorder selected from the group consisting of strokes, tumors, ischemia, Parkinson's disease, amyotrophic lateral sclerosis and migraines.

4. A reversible inhibitor of dipeptidyl peptidase IV, wherein the inhibitor has a core structure of:



, wherein:

X is CR<sub>2</sub>R<sub>3</sub>, O, S, or NR<sub>4</sub>; with the proviso that if X is S, or if X and X<sub>1</sub> are both CH<sub>2</sub>, and Z is O, and A is CN, and R<sub>1</sub> is H, then R is not NH substituted with C<sub>1</sub>-C<sub>9</sub> straight or branched chain alkyl, or NH substituted with C<sub>3</sub>-C<sub>7</sub> cycloalkyl;

X<sub>1</sub> is CR<sub>2</sub>R<sub>3</sub>, O, S, or NR<sub>4</sub> with the proviso that X and X<sub>1</sub> cannot both be a heteroatom, and with the proviso that if X and X<sub>1</sub> are both CH<sub>2</sub>, and Z is O, and R<sub>1</sub> is NH<sub>2</sub>, then R is not 1-methylpropyl if A is COOH, and R is not cyclopentyl if A is CN;

A is H, COOH, or isosteres of carboxylic acids, such as one selected from the group consisting of CN, SO<sub>3</sub>H, CONOH, PO<sub>3</sub>R<sub>5</sub>R<sub>6</sub>, SO<sub>2</sub>NHR<sub>7</sub>, tetrazole, amides, esters, and acid anhydrides, with the proviso that if A is CN, and R<sub>1</sub> is NH<sub>2</sub>, and Z is O, and R is 1-methylpropyl, then X and X<sub>1</sub> are not both CH<sub>2</sub>; X and X<sub>1</sub> are not S; and X is not O;

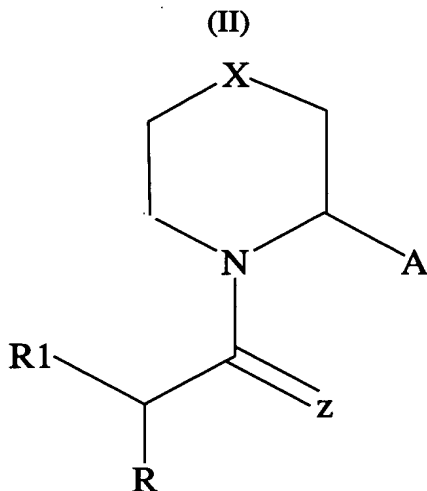
Z is O or S;

R and R<sub>1</sub> are independently selected from the group of functional groups consisting of H, C<sub>1</sub>-C<sub>9</sub> branched or straight chain alkyl, C<sub>2</sub>-C<sub>9</sub> branched or straight chain alkenyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, aryl, heteroaryl and amino, wherein any of the functional groups can be substituted with one or more of C<sub>1</sub>-C<sub>9</sub> straight or branched chain alkyl, aryl, heteroaryl, amino, halo, carbonyl, C<sub>1</sub>-C<sub>9</sub> alkoxy, C<sub>2</sub>-C<sub>9</sub> alkenyloxy, phenoxy, benzyloxy, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, cyano, amido, thiol, trifluoromethyl, or hydroxy, wherein each of R and R<sub>1</sub> can be the same or different; and

R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub>, if present, are independently selected from the group of functional groups consisting of H, C<sub>1</sub>-C<sub>9</sub> branched or straight chain alkyl, C<sub>2</sub>-C<sub>9</sub> branched or straight chain alkenyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, aryl, heteroaryl and amino, wherein any of the functional groups can be substituted with one or more of C<sub>1</sub>-C<sub>9</sub> straight or branched chain alkyl, aryl, heteroaryl, amino, halo, carbonyl, C<sub>1</sub>-C<sub>9</sub> alkoxy, C<sub>2</sub>-C<sub>9</sub> alkenyloxy, phenoxy, benzyloxy, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, cyano, amido, thiol, trifluoromethyl, or hydroxy, wherein each of R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub>, if present, can be the same or different.

5. The reversible inhibitor according to claim 4, wherein the inhibitor possesses an IC<sub>50</sub> of no more than 1  $\mu$ m and has a molecular weight of no more than 500.

6. A reversible inhibitor of dipeptidyl peptidase IV, wherein the inhibitor has a core structure of:



, wherein:

X is CR<sub>2</sub>R<sub>3</sub>, O, S, or NR<sub>4</sub>;

A is H, COOH, or isosteres of carboxylic acids, such as one selected from the group consisting of CN, SO<sub>3</sub>H, CONOH, PO<sub>3</sub>R<sub>5</sub>R<sub>6</sub>, SO<sub>2</sub>NHR<sub>7</sub>, tetrazole, amides, esters, and acid anhydrides;

Z is O or S;

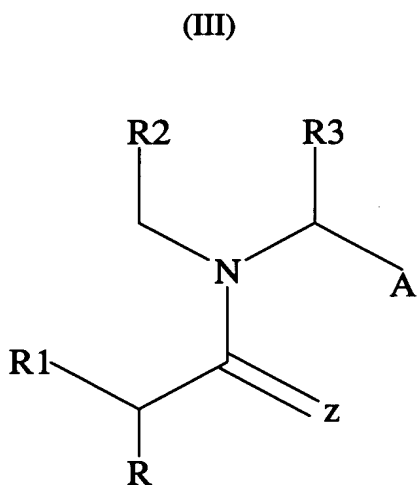
R and R<sub>1</sub> are independently selected from the group of functional groups consisting of H, C<sub>1</sub>-C<sub>9</sub> branched or straight chain alkyl, C<sub>2</sub>-C<sub>9</sub> branched or straight chain alkenyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, aryl, heteroaryl and amino, wherein any of the functional groups can be substituted with one or more of C<sub>1</sub>-C<sub>9</sub> straight or branched chain alkyl, aryl, heteroaryl, amino, halo, carbonyl, C<sub>1</sub>-C<sub>9</sub> alkoxy, C<sub>2</sub>-C<sub>9</sub> alkenyloxy, phenoxy, benzyloxy, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, cyano, amido, thiol, trifluoromethyl, or hydroxy, wherein each of R and R<sub>1</sub> can be the same or different; and

R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub>, if present, are independently selected from the group of functional groups consisting of H, C<sub>1</sub>-C<sub>9</sub> branched or straight chain alkyl, C<sub>2</sub>-C<sub>9</sub> branched or straight chain alkenyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, aryl, heteroaryl and amino, wherein any of the functional groups can be substituted with one or more of C<sub>1</sub>-C<sub>9</sub> straight or branched chain alkyl, aryl, heteroaryl, amino, halo, carbonyl, C<sub>1</sub>-C<sub>9</sub> alkoxy, C<sub>2</sub>-C<sub>9</sub> alkenyloxy, phenoxy, benzyloxy, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, cyano, amido, thiol,

trifluoromethyl, or hydroxy, wherein each of R2, R3, R4, R5, R6 and R7, if present, can be the same or different.

7. The reversible inhibitor according to claim 6, wherein the inhibitor possesses an  $IC_{50}$  of no more than 1  $\mu$ m and has a molecular weight of no more than 500.

8. A reversible inhibitor of dipeptidyl peptidase IV, wherein the inhibitor has a core structure of:



, wherein:

A is H, COOH, or isosteres of carboxylic acids, such as one selected from the group consisting of CN, SO<sub>3</sub>H, CONOH, PO<sub>3</sub>R5R6, SO<sub>2</sub>NHR7, tetrazole, amides, esters, and acid anhydrides;

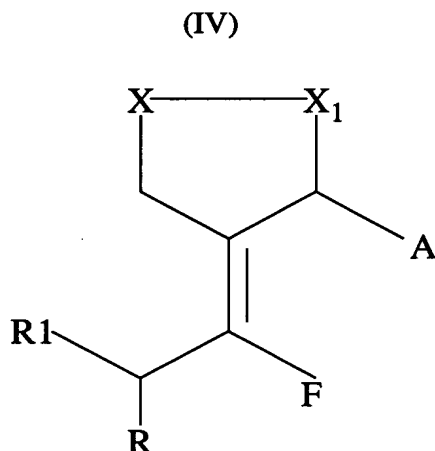
Z is O or S;

R, R1, R2 and R3 are independently selected from the group of functional groups consisting of H, C<sub>1</sub>-C<sub>9</sub> branched or straight chain alkyl, C<sub>2</sub>-C<sub>9</sub> branched or straight chain alkenyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, aryl, heteroaryl and amino, wherein any of the functional groups can be substituted with one or more of C<sub>1</sub>-C<sub>9</sub> straight or branched chain alkyl, aryl, heteroaryl, amino, halo, carbonyl, C<sub>1</sub>-C<sub>9</sub> alkoxy, C<sub>2</sub>-C<sub>9</sub> alkenyloxy, phenoxy, benzyloxy, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, cyano, amido, thiol, trifluoromethyl, or hydroxy, wherein each of R, R1, R2 and R3 can be the same or different; and

R4, R5, R6 and R7, if present, are independently selected from the group of functional groups consisting of H, C<sub>1</sub>-C<sub>9</sub> branched or straight chain alkyl, C<sub>2</sub>-C<sub>9</sub> branched or straight chain alkenyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, aryl, heteroaryl and amino, wherein any of the functional groups can be substituted with one or more of C<sub>1</sub>-C<sub>9</sub> straight or branched chain alkyl, aryl, heteroaryl, amino, halo, carbonyl, C<sub>1</sub>-C<sub>9</sub> alkoxy, C<sub>2</sub>-C<sub>9</sub> alkenyloxy, phenoxy, benzyloxy, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, cyano, amido, thiol, trifluoromethyl, or hydroxy, wherein each of R4, R5, R6 and R7, if present, can be the same or different.

9. The reversible inhibitor according to claim 8, wherein the inhibitor possesses an IC<sub>50</sub> of no more than 1  $\mu$ m and has a molecular weight of no more than 500.

10. A reversible inhibitor of dipeptidyl peptidase IV, wherein the inhibitor has a core structure of:



, wherein:

X is CR<sub>2</sub>R<sub>3</sub>, O, S, or NR<sub>4</sub>;

X<sub>1</sub> is CR<sub>2</sub>R<sub>3</sub>, O, S, or NR<sub>4</sub> with the proviso that X and X<sub>1</sub> cannot both be a heteroatom;

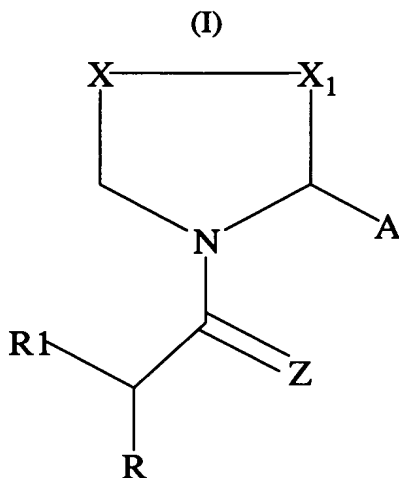
A is H, COOH, or isosteres of carboxylic acids, such as one selected from the group consisting of CN, SO<sub>3</sub>H, CONOH, PO<sub>3</sub>R<sub>5</sub>R<sub>6</sub>, SO<sub>2</sub>NHR<sub>7</sub>, tetrazole, amides, esters, and acid anhydrides;

R and R<sub>1</sub> are independently selected from the group of functional groups consisting of H, C<sub>1</sub>-C<sub>9</sub> branched or straight chain alkyl, C<sub>2</sub>-C<sub>9</sub> branched or straight chain alkenyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, aryl, heteroaryl and amino, wherein any of the functional groups can be substituted with one or more of C<sub>1</sub>-C<sub>9</sub> straight or branched chain alkyl, aryl, heteroaryl, amino, halo, carbonyl, C<sub>1</sub>-C<sub>9</sub> alkoxy, C<sub>2</sub>-C<sub>9</sub> alkenyloxy, phenoxy, benzyloxy, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, cyano, amido, thiol, trifluoromethyl, or hydroxy, wherein each of R and R<sub>1</sub> can be the same or different; and

R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub>, if present, are independently selected from the group of functional groups consisting of H, C<sub>1</sub>-C<sub>9</sub> branched or straight chain alkyl, C<sub>2</sub>-C<sub>9</sub> branched or straight chain alkenyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, aryl, heteroaryl and amino, wherein any of the functional groups can be substituted with one or more of C<sub>1</sub>-C<sub>9</sub> straight or branched chain alkyl, aryl, heteroaryl, amino, halo, carbonyl, C<sub>1</sub>-C<sub>9</sub> alkoxy, C<sub>2</sub>-C<sub>9</sub> alkenyloxy, phenoxy, benzyloxy, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, cyano, amido, thiol, trifluoromethyl, or hydroxy, wherein each of R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub>, if present, can be the same or different.

11. The reversible inhibitor according to claim 10, wherein the inhibitor possesses an IC<sub>50</sub> of no more than 1  $\mu$ m and has a molecular weight of no more than 500.

12. A method of treating a patient having a disorder of the central nervous system, comprising administering to the patient a therapeutically effective amount of a reversible inhibitor of dipeptidyl peptidase IV, wherein the inhibitor has a core structure of:



, wherein:

X is CR<sub>2</sub>R<sub>3</sub>, O, S, or NR<sub>4</sub>;

X<sub>1</sub> is CR<sub>2</sub>R<sub>3</sub>, O, S, or NR<sub>4</sub> with the proviso that X and X<sub>1</sub> cannot both be a heteroatom;

A is H, COOH, or isosteres of carboxylic acids, such as, one selected from the group consisting of CN, SO<sub>3</sub>H, CONOH, PO<sub>3</sub>R<sub>5</sub>R<sub>6</sub>, SO<sub>2</sub>NHR<sub>7</sub>, tetrazole, amides, esters, and acid anhydrides;

Z is O or S;

R and R<sub>1</sub> are independently selected from the group of functional groups consisting of H, C<sub>1</sub>-C<sub>9</sub> branched or straight chain alkyl, C<sub>2</sub>-C<sub>9</sub> branched or straight chain alkenyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, aryl, heteroaryl and amino, wherein any of the functional groups can be substituted with one or more of C<sub>1</sub>-C<sub>9</sub> straight or branched chain alkyl, aryl, heteroaryl, amino, halo, carbonyl, C<sub>1</sub>-C<sub>9</sub> alkoxy, C<sub>2</sub>-C<sub>9</sub> alkenyloxy, phenoxy, benzyloxy, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, cyano, amido, thiol, trifluoromethyl, or hydroxy, wherein each of R and R<sub>1</sub> can be the same or different; and

R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub>, if present, are independently selected from the group of functional groups consisting of H, C<sub>1</sub>-C<sub>9</sub> branched or straight chain alkyl, C<sub>2</sub>-C<sub>9</sub> branched or straight chain alkenyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, aryl, heteroaryl and amino, wherein any of the functional groups can be substituted with one or more of C<sub>1</sub>-

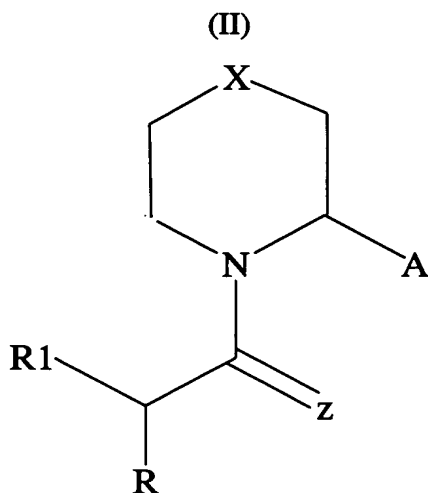
C<sub>9</sub> straight or branched chain alkyl, aryl, heteroaryl, amino, halo, carbonyl, C<sub>1</sub>-C<sub>9</sub> alkoxy, C<sub>2</sub>-C<sub>9</sub> alkenyloxy, phenoxy, benzyloxy, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, cyano, amido, thiol, trifluoromethyl, or hydroxy, wherein each of R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub>, if present, can be the same or different.

13. The method according to claim 12, wherein the inhibitor possesses an IC<sub>50</sub> of no more than 1  $\mu$ m and has a molecular weight of no more than 500.

14. The method according to claim 12, wherein if X is S, or if X and X1 are both CH<sub>2</sub>, and Z is O, and A is CN, and R1 is H, then R is not NH substituted with C1-C9 straight or branched chain alkyl, or NH substituted with C3-C7 cycloalkyl; and if X and X1 are both CH<sub>2</sub>, and Z is O, and R1 is NH<sub>2</sub>, then R is not 1-methylpropyl if A is COOH, and R is not cyclopentyl if A is CN; and if A is CN, and R1 is NH<sub>2</sub>, and Z is O, and R is 1-methylpropyl, then X and X1 are not both CH<sub>2</sub>; X and X1 are not S; and X is not O;



15. A method of treating a patient having a disorder of the central nervous system, comprising administering to the patient a therapeutically effective amount of a reversible inhibitor of dipeptidyl peptidase IV, wherein the inhibitor has a core structure of:



, wherein:

X is CR<sub>2</sub>R<sub>3</sub>, O, S, or NR<sub>4</sub>;

A is H, COOH, or isosteres of carboxylic acids, such as one selected from the group consisting of CN, SO<sub>3</sub>H, CONOH, PO<sub>3</sub>R<sub>5</sub>R<sub>6</sub>, SO<sub>2</sub>NHR<sub>7</sub>, tetrazole, amides, esters, and acid anhydrides;

Z is O or S;

R and R<sub>1</sub> are independently selected from the group of functional groups consisting of H, C<sub>1</sub>-C<sub>9</sub> branched or straight chain alkyl, C<sub>2</sub>-C<sub>9</sub> branched or straight chain alkenyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, aryl, heteroaryl and amino, wherein any of the functional groups can be substituted with one or more of C<sub>1</sub>-C<sub>9</sub> straight or branched chain alkyl, aryl, heteroaryl, amino, halo, carbonyl, C<sub>1</sub>-C<sub>9</sub> alkoxy, C<sub>2</sub>-C<sub>9</sub> alkenyloxy, phenoxy, benzyloxy, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, cyano, amido, thiol, trifluoromethyl, or hydroxy, wherein each of R and R<sub>1</sub> can be the same or different; and

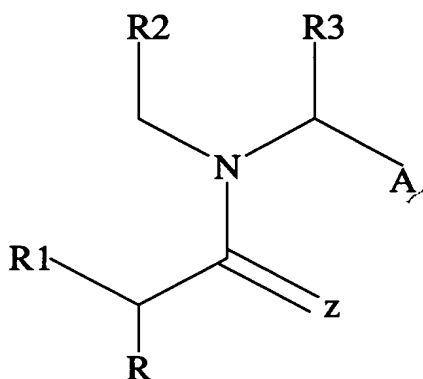
R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub>, if present, are independently selected from the group of functional groups consisting of H, C<sub>1</sub>-C<sub>9</sub> branched or straight chain alkyl, C<sub>2</sub>-C<sub>9</sub> branched or straight chain alkenyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, aryl, heteroaryl and amino, wherein any of the functional groups can be substituted with one or more of C<sub>1</sub>-C<sub>9</sub> straight or branched chain alkyl, aryl, heteroaryl, amino, halo, carbonyl, C<sub>1</sub>-C<sub>9</sub> alkoxy,

C<sub>2</sub>-C<sub>9</sub> alkenyloxy, phenoxy, benzyloxy, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, cyano, amido, thiol, trifluoromethyl, or hydroxy, wherein each of R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub>, if present, can be the same or different.

16. The method according to claim 15, wherein the inhibitor possesses an IC<sub>50</sub> of no more than 1  $\mu$ m and has a molecular weight of no more than 500.

17. A method of treating a patient having a disorder of the central nervous system, comprising administering to the patient a therapeutically effective amount of a reversible inhibitor of dipeptidyl peptidase IV, wherein the inhibitor has a core structure of:

(III)



, wherein

A is H, COOH, or isosteres of carboxylic acids, such as one selected from the group consisting of CN, SO<sub>3</sub>H, CONOH, PO<sub>3</sub>R<sub>5</sub>R<sub>6</sub>, SO<sub>2</sub>NHR<sub>7</sub>, tetrazole, amides, esters, and acid anhydrides;

Z is O or S;

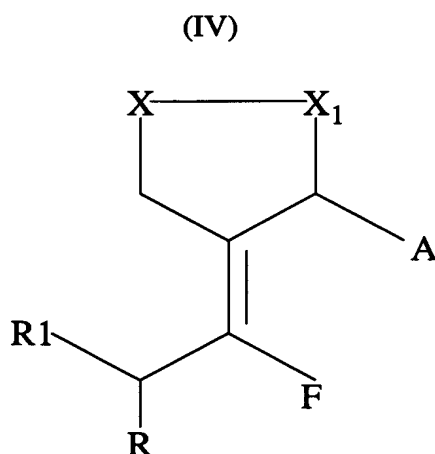
R, R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> are independently selected from the group of functional groups consisting of H, C<sub>1</sub>-C<sub>9</sub> branched or straight chain alkyl, C<sub>2</sub>-C<sub>9</sub> branched or straight chain alkenyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, aryl, heteroaryl and amino, wherein any of the functional groups can be substituted with one or more of C<sub>1</sub>-C<sub>9</sub> straight or branched chain alkyl, aryl, heteroaryl, amino, halo, carbonyl, C<sub>1</sub>-C<sub>9</sub> alkoxy, C<sub>2</sub>-C<sub>9</sub> alkenyloxy,

phenoxy, benzyloxy, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, cyano, amido, thiol, trifluoromethyl, or hydroxy, wherein each of R, R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> can be the same or different; and

R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub>, if present, are independently selected from the group of functional groups consisting of H, C<sub>1</sub>-C<sub>9</sub> branched or straight chain alkyl, C<sub>2</sub>-C<sub>9</sub> branched or straight chain alkenyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, aryl, heteroaryl and amino, wherein any of the functional groups can be substituted with one or more of C<sub>1</sub>-C<sub>9</sub> straight or branched chain alkyl, aryl, heteroaryl, amino, halo, carbonyl, C<sub>1</sub>-C<sub>9</sub> alkoxy, C<sub>2</sub>-C<sub>9</sub> alkenyloxy, phenoxy, benzyloxy, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, cyano, amido, thiol, trifluoromethyl, or hydroxy, wherein each of R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub>, if present, can be the same or different.

18. The method according to claim 17, wherein the inhibitor possesses an IC<sub>50</sub> of no more than 1  $\mu$ m and has a molecular weight of no more than 500.

19. A method of treating a patient having a disorder of the central nervous system, comprising administering to the patient a therapeutically effective amount of a reversible inhibitor of dipeptidyl peptidase IV, wherein the inhibitor has a core structure of:



, wherein:

X is CR<sub>2</sub>R<sub>3</sub>, O, S, or NR<sub>4</sub>;

X<sub>1</sub> is CR<sub>2</sub>R<sub>3</sub>, O, S, or NR<sub>4</sub> with the proviso that X and X<sub>1</sub> cannot both be a heteroatom;

A is H, COOH, or isosteres of carboxylic acids, such as one selected from the group consisting of CN, SO<sub>3</sub>H, CONOH, PO<sub>3</sub>R<sub>5</sub>R<sub>6</sub>, SO<sub>2</sub>NHR<sub>7</sub>, tetrazole, amides, esters, and acid anhydrides;

R and R<sub>1</sub> are independently selected from the group of functional groups consisting of H, C<sub>1</sub>-C<sub>9</sub> branched or straight chain alkyl, C<sub>2</sub>-C<sub>9</sub> branched or straight chain alkenyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, aryl, heteroaryl and amino, wherein any of the functional groups can be substituted with one or more of C<sub>1</sub>-C<sub>9</sub> straight or branched chain alkyl, aryl, heteroaryl, amino, halo, carbonyl, C<sub>1</sub>-C<sub>9</sub> alkoxy, C<sub>2</sub>-C<sub>9</sub> alkenyloxy, phenoxy, benzyloxy, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, cyano, amido, thiol, trifluoromethyl, or hydroxy, wherein each of R and R<sub>1</sub> can be the same or different; and

R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub>, if present, are independently selected from the group of functional groups consisting of H, C<sub>1</sub>-C<sub>9</sub> branched or straight chain alkyl, C<sub>2</sub>-C<sub>9</sub> branched or straight chain alkenyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, aryl, heteroaryl and amino, wherein any of the functional groups can be substituted with one or more of C<sub>1</sub>-C<sub>9</sub> straight or branched chain alkyl, aryl, heteroaryl, amino, halo, carbonyl, C<sub>1</sub>-C<sub>9</sub> alkoxy, C<sub>2</sub>-C<sub>9</sub> alkenyloxy, phenoxy, benzyloxy, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, cyano, amido, thiol, trifluoromethyl, or hydroxy, wherein each of R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub>, if present, can be the same or different.

20. The method according to claim 19, wherein the inhibitor possesses an IC<sub>50</sub> of no more than 1  $\mu$ m and has a molecular weight of no more than 500.

21. A method of treating a patient having a disorder of the central nervous system, comprising administering to the patient a therapeutically effective amount of a inhibitor of dipeptidyl peptidase IV.

22. The method according to claim 21, wherein the inhibitor comprises a proline mimetic and possesses an IC<sub>50</sub> of no more than 1  $\mu$ m and has a molecular weight of no more than 700.

23. The method according to claim 21, wherein the inhibitor has a core structure selected from the group consisting of Core Structure I, Core Structure II, Core Structure III and Core Structure IV.

24. The method according to claim 21, wherein the inhibitor is reversible.

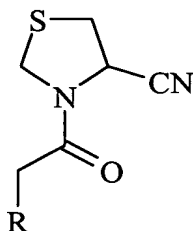
25. The method according to claim 21, wherein the central nervous system disorder is selected from the group consisting of strokes, tumors, ischemia, Parkinson's disease, amyotrophic lateral sclerosis and migraines.

26. A method of treating a patient having a disorder selected from the group consisting of strokes, tumors, ischemia, Parkinson's disease, memory loss, hearing loss, vision loss, migraines, brain injury, spinal cord injury, Alzheimer's disease, amyotrophic lateral, multiple sclerosis, diabetic neuropathy and prostate abnormalities, wherein the method comprises administering to the patient a therapeutically effective amount of a inhibitor of dipeptidyl peptidase IV.

27. A method according to claim 26, wherein the inhibitor comprises a proline mimetic and possesses an  $IC_{50}$  of no more than  $1 \mu m$  and has a molecular weight of no more than 700.

28. The method according to claim 26, wherein the inhibitor has a core structure selected from the group consisting of Core Structure I, Core Structure II, Core Structure III and Core Structure IV.

29. A method of using a reversible inhibitor of DPP-IV, comprising administering to a human patient suffering from a central nervous system disorder a pharmaceutically effective amount of the inhibitor, wherein the inhibitor is



wherein R is NH-R<sup>I</sup>;

R<sup>I</sup> is: C<sub>1</sub> - C<sub>12</sub> straight or branched chain alkyl;

C<sub>3</sub> - C<sub>7</sub> cycloalkyl;

CH<sub>2</sub>- CH<sub>2</sub>-NH-R<sup>II</sup>;

CH<sub>2</sub>- CH<sub>2</sub>-R<sup>III</sup>;

CH<sub>2</sub>- CH<sub>2</sub>-CHR<sup>IV</sup>- R<sup>IV</sup>; or

CH<sub>2</sub>- CH<sub>2</sub>-CH<sub>2</sub>-R<sup>V</sup>;

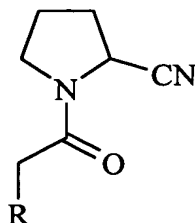
R<sup>II</sup> is a pyridine ring optionally substituted in one or two positions with halo, trifluoromethyl, cyano or nitro; or a pyrimidine ring optionally substituted in one position with halo, trifluoromethyl, cyano or nitro;

R<sup>III</sup> is a phenyl ring optionally substituted in one to three positions with halo or C<sub>1</sub> - C<sub>3</sub> alkoxy;

Each R<sup>IV</sup> is independently a phenyl ring optionally substituted in one position with halo or C<sub>1</sub> - C<sub>3</sub> alkoxy; and

R<sup>V</sup> is a 2-oxopyrrolidine group or a C<sub>2</sub> - C<sub>4</sub> alkoxy group.

30. A method of using a reversible inhibitor of DPP-IV, comprising administering to a human patient suffering from a central nervous system disorder a pharmaceutically effective amount of the inhibitor, wherein the inhibitor is



wherein R is NH-R<sup>I</sup>;

R<sup>I</sup> is: C<sub>1</sub> - C<sub>12</sub> straight or branched chain alkyl optionally substituted with hydroxy, acetyl, C<sub>1</sub> - C<sub>3</sub> alkoxy, or C<sub>1</sub> - C<sub>3</sub> hydroxyalkyl;

C<sub>3</sub> - C<sub>12</sub> cycloalkyl optionally substituted with hydroxyl, acetyl, C<sub>1</sub> - C<sub>3</sub> alkoxy, or C<sub>1</sub> - C<sub>3</sub> hydroxyalkyl;

adamantyl; indanyl; piperidyl optionally substituted with benzyl; pyrrolidine optionally substituted with benzyl; bicycloheptyl optionally substituted in one to three positions with methyl; phenyl optionally substituted with in one to three positions with halo, methoxy, trifluoromethyl; pyridyl optionally substituted in one to three positions with halo, trifluoromethyl, nitro; or pyrimidyl optionally substituted with halo, trifluoromethyl, nitro;

C<sub>1</sub> - C<sub>3</sub> straight or branched chain alkyl substituted with R<sup>IV</sup>, and optionally substituted with hydroxy; or

(CH<sub>2</sub>)<sub>1-3</sub> - NR<sup>II</sup>R<sup>III</sup>;

R<sup>II</sup> is hydrogen or methyl;

R<sup>III</sup> is phenyl optionally substituted with CN, or pyridyl optionally substituted with CN; and

R<sup>IV</sup> is a group selected from phenyl, naphthyl, cyclohexenyl, pyridyl, pyrimidyl, adamantyl, phenoxy, wherein the group is optionally substituted in one to two positions with ethoxy, methoxy, halo, phenylsulfide, or phenylsulfide substituted with hydroxymethyl.